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May 17, 2004

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APPLICATION NUMBER: 60/458,922 —

FILING DATE: March 28, 2003 -

RELATED PCT APPLICATION NUMBER: PCT/US04/09384

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By Authority of the COMMISSIONER OF PATENTS AND TRADEMARKS

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"PROVISIONAL APPLICATION FOR PATENT COVER SHEET (Large Entity)

This is a request for filing a PROVISIONAL APPLICATION FOR PATENT under 37 CFR 1.53 (c).

INVENTOR(S)/APPLICANT(S)					—				
Given Name (first and middle [if any]) Family Name or Sumame Residence (City and either State or Foreign Country)									
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USE ONLY FOR FILING A PROVISIONAL APPLICATION FOR PATENT

PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application:

Nicholas Bodor

Serial Number:

Not Yet Assigned March 28, 2003.

Filing Date: Title:

ORAL AND TRANSMUCOSAL DELIVERY OF

CYCLODEXTRIN BASED FORMULATIONS

Docket Number:

IVAX0012-P-USA

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Date of Deposit March 28, 2003

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Jeffrey J. Miller

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BOX PROVISIONAL PATENT APPLICATION

Assistant Commissioner for Patents Washington, DC 20231

Dear Sir:

TRANSMITTAL LETTER

Transmitted herewith for filing are the following documents:

- [| Provisional Application for Patent Cover Sheet (Large Entity);
- Provisional Patent Application (5 Pages Specification, 18 Pages Appendix);
- [] Authorization to charge Deposit Amount for filing fee of \$160.00; and
- [| Return Postcard

If the enclosed papers are considered incomplete, the Mail Room and/or the Application Branch is respectfully requested to contact the undersigned collect at (617) 535-4421, Boston, MA.

The Commissioner is hereby authorized to charge any additional fees which may be required or credit any overpayment to Deposit Acct. No. 50-1133.

Dated: 3-28-03

Respectfully submitte

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Docket Number:

IVAX0012-P-USA

PROVISIONAL APPLICATION FOR PATENT COVER SHEET (Large Entity)

INVENTOR(S)/APPLICANT(S)							
Given Name (first and middle [if any])	Family Name or Sumame	Residence (city and either State or Foreign Country)					
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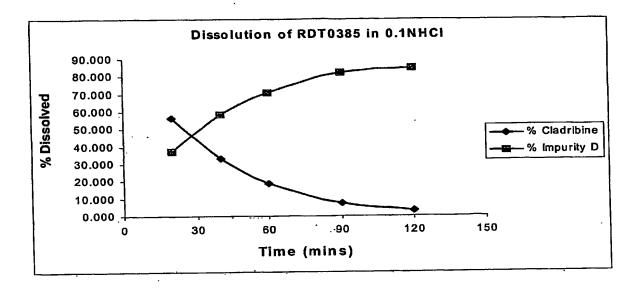
9 Cladribine freeze-dried Cyclodextrin complexes

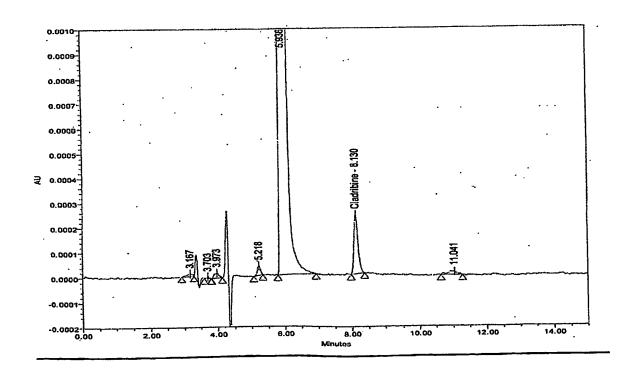
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1. API ANALYSIS

1.1 Dissolution in 0.1N HCl

Initial analysis of active by UV showed 10% degradation of API over 2 hours. Following from this HPLC analysis of active in 0.1N HCL showed degradation of Cladribine and growth of Impurity D (RRT 0.701). Approx 3% Cladribine remaining after 120 minutes dissolution.

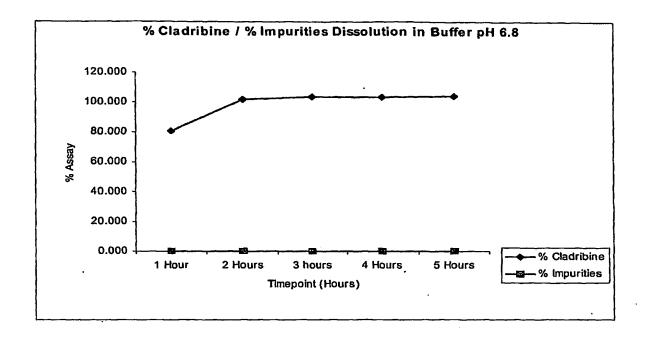




Chromatogram of Cladribine after 2 hours dissolution in 0.1N HCl. Growth of impurity D at retention time 5.936 minutes

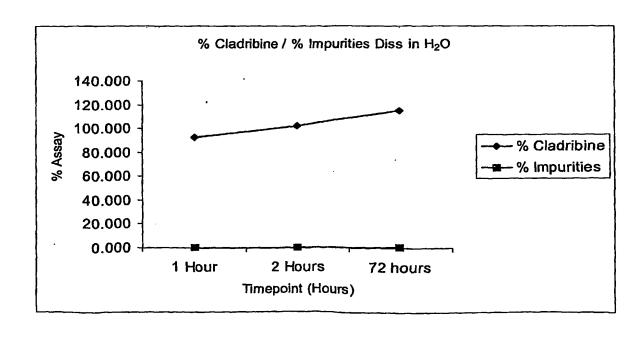
1.2 Dissolution in Phosphate buffer pH 6.8 (HPLC)

102% dissolved after 2 hours. No observed degradation after 5 hours. No increase in related substances.



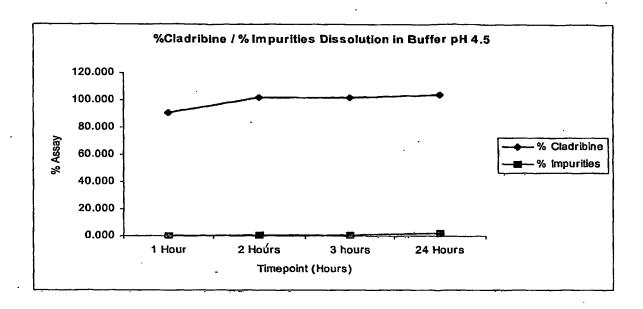
1.3 Dissolution in DI Water (HPLC)

102% dissolved after 2 hours. No observed degradation after 5 hours. Increase in assay of Cladribine after 72 hours due to evaporation of medium. No increase in related substances



1.4 Dissolution in Buffer pH 4.5 (HPLC)

102% dissolved after 2 hours. No observed degradation after 2 hours. Increase in impurities (0.1%) of Cladribine after 24 hours.



2 INTRINSIC DISSOLUTIONS

Note: IDR of 0.1 mg/min/cm² corresponds to solubility of 1 mg/ml.

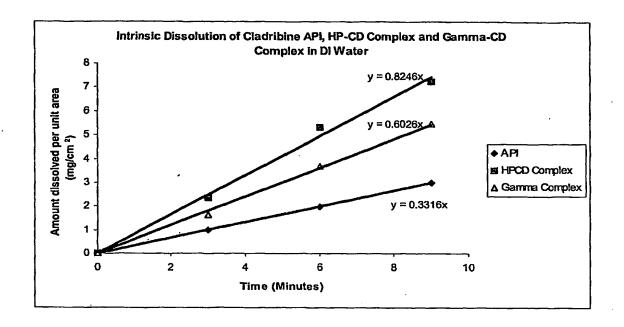
Cilag estimate solubility of 5mg/ml in water

IDR of API in DI water:

IDR of Gamma-CD complex in DI water:

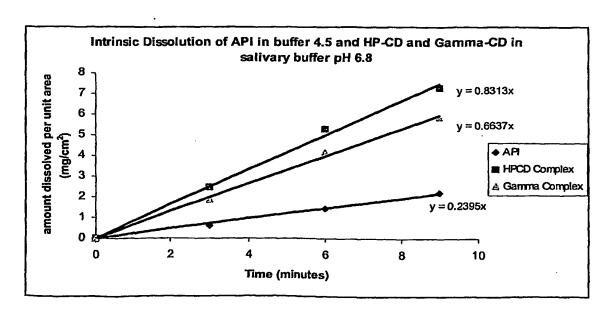
1DR of HP-CD complex in DI water:

0.3316 mg/min/cm²
0.6026 mg/min/cm²
0.8246 mg/min/cm²

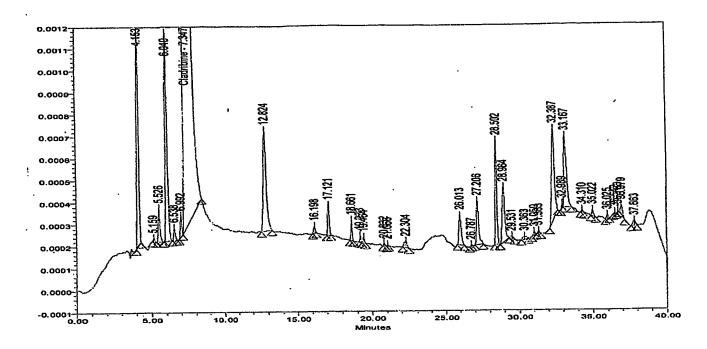


IDR of API in phosphate buffer pH 4.5: IDR of Gamma-CD complex in salivary buffer pH 7.0: IDR of HP-CD complex in salivary buffer pH 7.0: 0.2395 mg/min/cm² 0.6637 mg/min/cm² 0.8313 mg/min/cm²

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3. API RELATED SUBSTANCES



Name	Specification	RRT	Cilag Assay	IVAX Assay
2-Amino-2 deoxyadenosine (Impurity B)	NMT 0.3%	0.563	0.200	0.060
2-Chloro-adenine (Impurity D)	NMT 0.3%	0.701	<0.1	0.002
2-Methoxy-2-deoxyadenosine (Impurity E)	NMT 0.2%	0.821	0.200	0.082
2-Chloro-9-(2 deoxy-α-D- ribofuranosyl)-adenine (Impurity F)	NMT 0.2%	0.951	<0.1	0.01
Cladribine	98% - 102%	1.000	99.8	98.5
Unknown 1	NMT 0.1%	1.763		0.088
Unlnown Impurity RRT (Cilag RRT) = 1.85	NMT 0.2%	1.85		ND
Impurity G	NMT 0.1%	2.123		ND
RWJ-47753-000	NMT 0.1%	3.877		0.043
RWJ-47754-000	NMT 0.1%	4.511		0.056
TOTAL IMPURITIES	NMT 1.0%		0.6%	0.3%

4. FINISHED PRODUCT RELATED SUBSTANCES

Name	RRT	Specification	RDT0385 (Fludaribine formulation)	RDT0398a (Carbomer formulation)	RDT039 (Cyclode formulat
2-Amino-2 deoxyadenosine (Impurity B)	0.563	NMT 0.3%	0.059	0.067	0.056
2-Chloro-adenine (Impurity D)	0.701	NMT 0.3%	0.002	0.002	0.002
2-Methoxy-2- deoxyadenosine (Impurity E)	0.821	NMT 0.2%	0.083	0.093	0.076
2-Chloro-9-(2 deoxy-α- D-ribofuranosyl)- adenine (Impurity F)	0.951	NMT 0.2%	0.010	0.012	0.009
Cladribine	1.000	98% - 102%	96	114	90
Unknown 1	1.763	NMT 0.1%	0.086	0.101	0.082
Unlnown Impurity RRT (Cilag RRT) = 1.85		NMT 0,2%			
Impurity G	2.123	NMT 0.1%	0.001	0.000	0.000
RWJ-47753-000	3.877	NMT 0.1%	0.042	0.050	0.039
RWJ-47754-000	4.511	NMT 0.1%	0.049	0.059	0.047
TOTAL IMPURITIES		NMT 1.0%	0.33%	0.38%	0.24%

5. ASSAY AND RELATED SUBSTANCES OF FREEZED DRIED COMPLEX RAW MATERIAL AND TABLETS

Identity	Chemical Name	RRT	Gammá – CD Raw Material	HP-β-CD Raw Material	FD02 (5mg Gamma- CD Tablets)	FD03 (5mg HPCD Tablets)
Imp B	2-Amino-2'- deoxyadenosine	0.54	0.28	0.19	0.31	0.29
Imp D	2-Chloroadenine	0.73	<0.05	ND	ND	ND
Imp E	2-Methoxy-2'- deoxyadenosine	0.83	0.14	0.12	0.13	0.13
Imp F	2-Chloro-9-(2'- deoxy-α-D- ribofuranosyl)- adenine	0.93	ND	ND	ND	ND
API	Cladribine	1.00	108	100	105	102
Theoretical % Active in Complex	· Cladribine		2.128	2.347		
Actual % Active in Complex	Cladribine		2.293	2.353		
Unknown	Not Known	1.89	0.06	0.09	0.07	0.07
RWJ- 49616-000	Not Known	2.60	ND	ND	ND	ND
Unknown	Not Known	3.06	<0.05	1.56*	<0.05	<0,05
Unknown	Not Known	3.43	0.05	0.07	0.08	0.06
RWJ- 47753-000	Not Known	3.90	ND	ND	ND	ND
Unknown	Not Known	4.18	ND	ND	0.26	ND
Unknown	Not Known	4.39	ND	ND	0.98	0.31
Unknown	Not Known	4.63	ND	0.33	ND	ND
RWJ- 47754-000	Not Known	4.68	0.22	0.15	0.34	0.21
TOTAL			0.75	2.51	2.17	1.01

^{*} To be investigated. Possible solvent or carryover.



SUMMARY

No differences observed in assay for related substances for API and any formulations. Recommended PDA analysis on API also.

6. FORMULATIONS BASED ON FLUDARIBINE

Three 100g batches using Cladribine API have been manufactured using the following formulations:

Batch	RDT0385	RDT0398a	RDT0398b2
	Fludaribine	Carbomer :	Cyclodextrin .
學的意思是是		Formulation :	Formulation
Ingredient ang/batch.	Faiffeld 2019		
Cladribine API	10.00	10.00	10.00
Hydroxypropyl fl Cyclodextrin			41.79
Carbonier 97/4P		20.00	
Avicel PHIONES	21.80	16.7	11.25
Lactose DC lil.	65.00	50.1	33.76
Grosacarmellose Sodium	2.00	2.00	2.00
Collidol Silicon Dioxide	0.20	0.20	0.20
Magnesium Sterate	1.00	1.00	1.00
Total .	100.00	100.00	100.00

Measurement	RDI70385	RDT0398a	RDT0398b
是是是第二条数据的。 第二条数据:	(IR)	(20% Garbomer)	(Cyclodextrin)
Average tablet weight (mg)	100.1	101.1	103.3
Average Hardness (Kp)	4.9	4.4	3.7
Friability (%)	0.18	0.03	0.18
Thickness (min)	2.86	3.24	2.92
Disintegration (min)	0.50	> 15.00	6.60

6.1 Fludaribine Formulation: RDT0385

• Assay - 101.4%

CU - 100.5%, RSD = 3.17%
 UV Dissolution (0.1N HCl) - Max 91% 30 minutes.

HPLC analysis carried out on dissolution in HCl showed breakdown of Cladribine into impurity
 D. Only 3% Cladribine remaining after 2 hours dissolution.

UV Dissolution (buffer pH 6.8)
 Slow release. 85% after 240 minutes

• UV Dissolution (Water) - Fast release, 101% after 2 hours.

6.2 Enteric-coated tablets: (Fludaribine Formulation). RDT0385b

- UV Dissolution in 0.1N HCl followed by buffer pH 6.8 7.0.
- 7% dissolution after 2 hours in acid, (min 5%, max 18%). On addition of pH 7.0 conditions dissolution increased to 97% after 2 hours (min 84%, Max 107%). After 4 hours in acid, dissolution was 116%.

6.3 20% Carbomer Formulation: RDT0398a

Results may be related to tablet weight i.e. heavier tablet gives higher dissolutions

• Assay - 113.9%

• CU - 105.7%, RSD = 6.4%. One result at 123.1%

• UV Dissolution (0.1N HCl) - Max 80%, 240 minutes. Slow release profile

• UV Dissolution (buffer pH 6.8) - Slow release. 86% after 10 hours. 0.1%

Carbomer interference. Further HPLC analysis shows possible Carbomer peak at 4-5 minutes.

0.2% - 1.0%.

• UV Dissolution (Water) - Fast release. 97% after 2 hours.

6.4 Cyclodextrin Formulation: RDT0398b

Cyclodextrin formulation is sub-potent due to extra Mag Stearate added. Estimated potency at 95%.

• Assay - 89.9%

• CU - 83.2%, RSD = 3.3%

UV Dissolution (0.1N HCl)
 Max 83%, 48 minutes. Degradation occurs.

• UV Dissolution (buffer pH 6.8) - Max 76%, 1 hour. No Cyclodextrin interference

UV Dissolution (Water)
 Max 86% after 1 hour.

SUMMARY

- Cladribine API is acid labile. Formulation needed to avoid acidic stomach conditions.
- No degradation observed in water, buffer pH 4.5 and buffer pH 6.8
- API IDR matches Cilag estimated solubility. Best IDR in water.
- Solubility issue in buffer pH 6.8. Dissolution values are less than assay results.
- Solubility does not seem to be a problem in water. Dissolution results matching assay and CU.
- Fludaribine formulation shows fast release in water and slow release in buffer pH 6.8.
- Carbomer formulation allows for slow release. Carbomer impurity (approx 1.0%) present in chromatography.



Some spurious CU results (121%) indicating possible processing problems with Carbomer 974P or high levels of Carbomer.

• Possible potency issue with Cyclodextrin formulation. Only getting 90% assay and dissolution. Immediate release in buffer and water.

7 BUCCAL AND GRANULE FORMULATIONS WITH DICLOFENAC API

Six batches using Diclofenac Sodium in place of Cladribine API were manufactured to explore the development of buccal / sublingual and mucoadhesive tablets as patentable cladribine formulations.

Formulation:

当	RDT0399a	#RDT039967	RDT0399d	RD 10399e	#RDT0399f	RDT0399g
	THE PARTY OF THE P		Granule 2			
	atablét		(Carbopol=			(Carbopol
Ingredient/			974P);	3974P)	\$1.7.7/1 G)\$5.50	
mg/tablet						
Diclofenac	10.00	10.00	10.00	10.00	10.00	10.00
Sodium CMG	2.50	5.00		が開発を開		
Sorbitol	87.00	84.50	是影響機能	是是過程	國理學國際	
Carbopol 974P	是一种	多是是是	2.50	10.00	集中型道	楚疆。西海巴
Carbopol 71G	2000年	阿爾斯里	の概念に関い	等於學語 麗	2.50	10.00
Avicel PH101	元 的是一种工作。		86.80	79.30	的 是阿姆克尔斯	記の世界中央を大力の
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Avicel PH102				19.30 第2.35章 66	21.75	19.88
AvicePH102- DactoseDGF15				79.30 16.20 16.30	21.75 65.25	19.88 59.63
THE PROPERTY OF THE PERSON OF			0.20	0.20		

^{*}Extra 0.5mg/tablet added to minimise picking. RDT0399c was manufactured as RDT0399a placebo.

Physical parameters:

as Measurement &	RDT0399a	** ;RDT03996	RDT03996	RDT0399g
Tooling//shape	Concave	Flat/Concave	Concave	Concave
Average tobletsweight (mg)	95.8	94.5	95.1	99.7
Average Hardness (Kp)	3.76	2.10	2.94	2.46
Eniability (%)	1.35	0.60	0.00	0.00
Thickness (mm)	3.07	2.90	2.95	3.10
Disintegration (min)	2min 34sec	4min 45sec	>15min*	>15min**

^{*}Tablet formed a soft globular mass with adhesive properties

NOTE: Diclofenac has solubility problems in 0.1N HCl. Diclofenac Na dissolves 16% - 20% in 0.1N HCl.

^{**} Tablet formed a globular mass with strong adhesive properties. Mass was dry in center after 15 mins.

7.1 Buccal / Sublingual:

RDT0399a + RDT0399b:

Manufactured using Sodium CMC at 2.5 - 5% respectively.

- UV Dissolution of approx 70% after 10 hours in simulated saliva solution. 68% dissolution after 30 minutes.
- Assay of 70%.
- No obvious reason for low results.
- Poor taste from tablets. Possible Diclofenac Na taste. Recommend 2mg drug formulation per 100
 mg tablet to inhibit possible taste issues.

7.2 Mucoadhesive granule for HGC fill:

NOTE:

Carbopol 71G may offer better flow properties due to its granular nature which may alleviate possible processing problems.

RDT0399d:

Manufactured using Carbopol 974P at 2.5%.

• 5% dissolution in 0.1N HCl after 2 hours. 97% dissolution after 3 hours in pH 7.0 buffer.

RDT0399e:

Manufactured using Carbopol 974P at 10%.

• 6% dissolution in 0.1N HCl after 2 hours. 91% - 99% after 3 hours in pH 7.0

7.3 Mucoadhesive Direct compression tablet:

RDT0399f:

Manufactured using Carbopol 71G at 2.5%.

• 5% dissolution in 0.1N HCl after 2 hours. 76% after 3 hours in pH 7.0

RDT0399g:

Manufactured using Carbopol 71G at 10%.

• 2% dissolution in 0.1N HCl after 2 hours. 90% after 3 hours in pH 7.0

All tablet formulations flowed and compressed well.

The granulated product produced a good strong granule. Milled through a 0.075 inch comil screen.

7.4 Tablet within a tablet formulation:

Outer tablet coat used to protect Cladribine from acidic stomach conditions.

Dissolution in 0.1N HCL followed by buffer pH 6.8. Tablets completely dissolved in acid (86% - 95%) after 25 minutes. No advantage.

8 PHASE SOLUBILITY TESTING

Table 1. Solubility of cyclodextrins in water (g/100 ml)

Temperatur e (°C)	ACD	BCD	GCD	HPCD
20.0	10.1	1.55	23.2	360.0
25.0	13.0	1.85	30.0	
30.0	16.0	2.25	38.5	
40.0	25.6	3.52	63.5	

PROTOCOL FOR PHASE SOLUBILITY STUDIES OF CLADRIBINE IN PRESENCE OF CYCLODEXTRIN

Reported Solubility of Cladribine in Water is 5 mg/ml

TABLE 1

SOLUTION SYSTEMS	Solution of CD, 800 mg in 4ml B.soln	DRUG ADDED
Α	2ml B. Soln (400 mg)	25 mg
В	2ml B.soln. + 2ml D.Water (200 mg)	25 mg
С	2 ml soln. B + 2 ml D.Water (100 mg)	25 mg
D	2 ml soln. C + 2 ml D.Water (50 mg)	25 mg
Е	2 ml soln. D + 2 ml D.Water (25 mg)* * Use only 2 ml of solution for testing	25 mg
F	2 ml D. Water (0.0 mg)	25 mg

Cyclodextrin

B.soln. - Bulk Solution

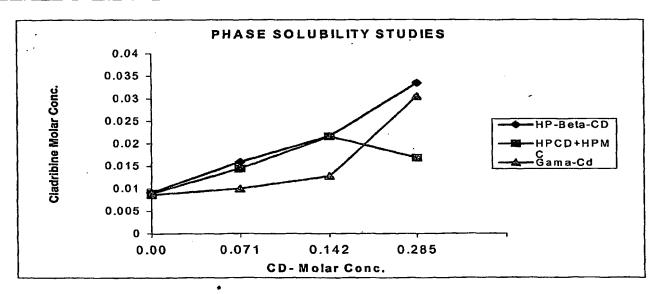
D. Water - Deionised Water

Method for preparation.

- 1. In screw capped vials take 2 ml Cyclodextrin solutions as mentioned in Table 1.
- 2. Add respective quantity of drug in each vial.
- 3. Allow the samples to sonicate for 30 minutes.
- 4. Remove the samples from sonicator and place on shaker for 8 hrs.
- 5. The sample after shaking is filtered to get clear supernant.
- 6. Analyse the sample by UV at 265 nm wavelength.

RESULTS:

CD Conc.	Onc. Cladribine -HP betaCD (Trial A)		Cladribine -HP betaCD + HPMC(0.1%) · (Trial B)			Cladribine -gama- CD (Trial C)			
CD Conc.	Absorbance	mg/mi	Molar concn.	Absorbance	mg/ml	Molar concn.	Absorbance	mg/ml	Molar c
0.00	0.140	2.610	0.0091	0.137	2.550	0.0089	0.132	2.459	0.0086
0.018	0.169	3.139	0.011	0.146	2.711	0.0095	0.1352	2.519	0.0088
0.035	0.191	3.554	0.0124	0.175	3.262	0.0114	0.1531	2.852	0.0100
0.071	0.245	4.570	0.016	0.223	4.149	0.0145	0.1542	2.873	0.0101
0.142	0.333	6.211	0.0217	0.332	6.185	0.0216	0.1965	3.661	0.0128
0.285	0.514	9.581	0.0335	0.259	4.831	0.0169	0.4688	8.733	0.0306



Observations:

- The best solubility results are obtained with HP-beta CD as complexing agent.
- With HP-beta CD + HPMC (0.1%) results are similar to HP-beta CD, at higher concentration fine precipitation was observed in the vials at the end of the study.
 - Absorbance of this sample is low and indicates precipitation of solubised drug
- Absorbance with Gama-Cyclodextrin is low as compared with HP-beta CD.
- Ball park solubility of 9.581 mg/ml in comparison to 5 mg/ml solubility with API alone.

SUMMARY

- Cyclodextrin/Cladribine complex showed increased Cladribine solubility
- Complex sent for freeze-drying.
- Cladribine API ground to decrease particle size (10g)
- Process buccal and sublingual tablets using freeze-dried material
 Issues regarding taste and poor assay, dissolution on previous buccal tablets.
 Information on buccal formulation work in Miami.
- Continued investigation into oral dosage formulations:
 - 1. Tablet-within-tablet:

High viscosity HPMC in outer formulation for protection against acidic stomach conditions.

2. Soft gel capsule:

10g API sent to Czechslovakia for trials.

3. Dry emulsion formulation:

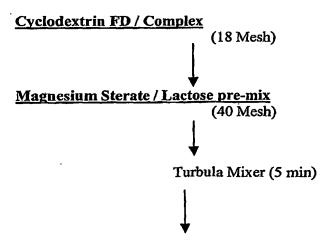
Dummy emulsion to be made with freeze-dried sample

9 CLADRIBINE FREEZE-DRIED CYCLODEXTRIN COMPLEXES

9.1 Cyclodextrin Complex Formulations for Buccal/Sublingual Dosage forms

	RODUCT		CD. Tablets	Sorbitol Tablets	Cladribine Complex	Gladribine Complex Tablets
	Batch No. Ingredient Gamma -CD	Lot no:		RDT 0418B	Pables PROTOSES Mg/Fables -	##RDTE0418D
FD-02	Gamma-CD +Cladribine	N/A	•	_	235	-
FD-03	HPCD + Cladribine	N/A	-	<u>-</u>	<u>-</u>	218
RE0484	Sorbitol	1F290	-	5.0	_	
RE0541	Magnesium Stearate	1C130	2.0	2.0	2.0	2.0

9.2 Manufacturing Process



Manesty Single station F-press (220 mg, 10.0 mm round concave UP/ Flat Bevelled LP)

OBSERVATIONS

Flow and compressibility good for all fractions.

No picking noticed

9.3 Physical Parameters

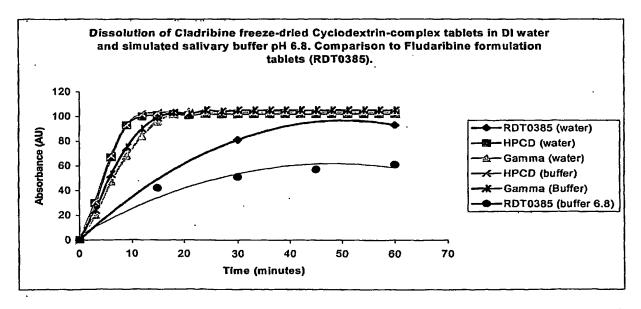
Average weight: A) 215 mg, B) 220 mg, C) 237mg, D)220mg.

Average Hardness: 3- 4 Kp

• Thickness: 3.2 mm - 3.4 mm

Disintegration Time: 6 – 7 minutes (Water/Simulated Saliva Buffer)

9.4 Dissolution profiles of freeze-dried buccal tablets in water and simulated salivary buffer solution



Simulated Saliva Solution: 2.38g Na₂HPO₄, 0.19g KH₂PO₄ and 8g NaCl in 1 litre of distilled water, pH 6.75, at 37°C

9.5 Results

• Increased Dissolution time.

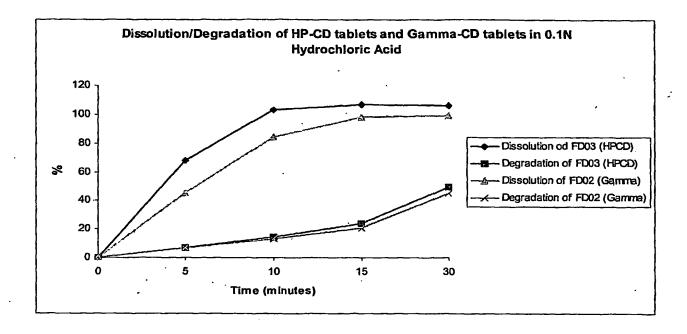
HP-CD. 100% dissolution in salivary buffer after 10 minutes. Gamma-CD. 100% dissolution in salivary buffer after 15 minutes

HP-CD. 100% dissolution in water after 10 minutes. Gamma-CD. 100% dissolution in salivary buffer after 15 - 18 minutes

Increased Solubility.

100% dissolution attained for both tablet types in both buffers. Comparison to Fludaribine formulation dissolution in water and buffer show faster dissolution and greater solubility.

9.6 Dissolution and Degradation profiles of freeze-dried Cladribine-Cyclodextrin complex buccal tablets in 0.1N HCl



- Degradation of Cladribine peak to Impurity D observed. 10 15% after 10 minutes. 100% dissolution after 10 15 minutes.
- By optimising complexation, we can further inhibit acidic degradation of the drug in the stomach whilst increasing drug availability for absorption.



APPENDIX

CONTENTS

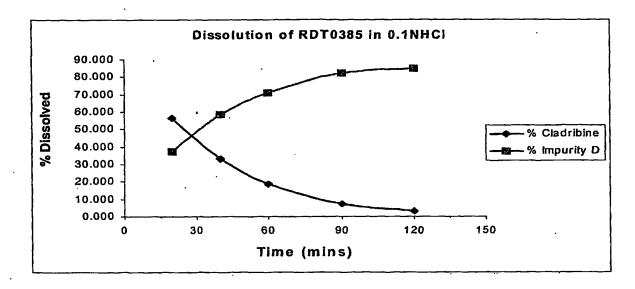
1. A	PI Dis	solution	ı Analysis
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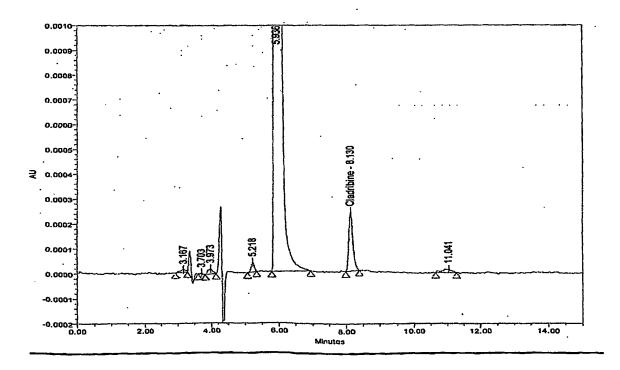
- 1.1 Dissolution in 0.1N HCl (UV and HPLC)
- 1.2 Dissolution in Phosphate buffer pH 6.8 (UV and HPLC)
- 1.3 Dissolution in DI Water (UV)
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 - 9.4 Dissolution profiles of Cladribine freeze-dried buccal tablets in water and salivary buffer
 - 9.5 Results
 - 9.6 Dissolution and Degradation profiles of Cladribine freeze-dried Cyclodextrin buccal tablets in 0.1N HCl

1. API ANALYSIS

1.1 Dissolution in 0.1N HCl

Initial analysis of active by UV showed 10% degradation of API over 2 hours, Following from this HPLC analysis of active in 0.1N HCL showed degradation of Cladribine and growth of Impurity D (RRT 0.701). Approx 3% Cladribine remaining after 120 minutes dissolution.

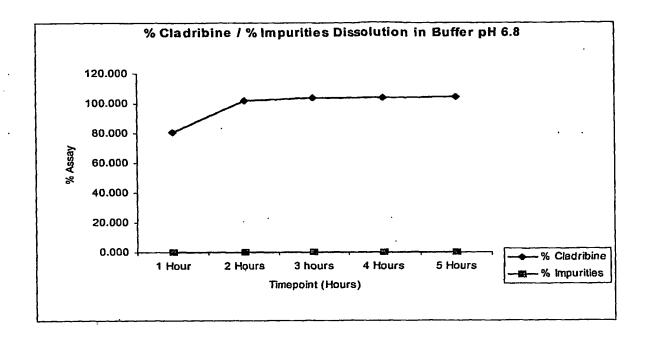




Chromatogram of Cladribine after 2 hours dissolution in 0.1N HCl. Growth of impurity D at retention time 5.936 minutes

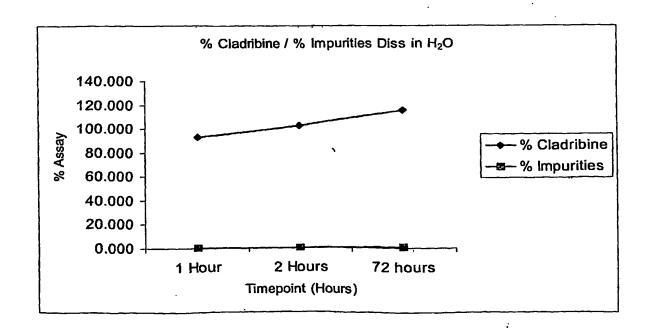
1.2 Dissolution in Phosphate buffer pH 6.8 (HPLC)

102% dissolved after 2 hours. No observed degradation after 5 hours. No increase in related substances.



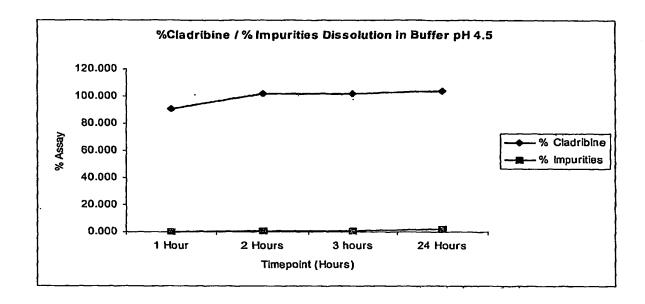
1.3 Dissolution in DI Water (HPLC)

102% dissolved after 2 hours. No observed degradation after 5 hours. Increase in assay of Cladribine after 72 hours due to evaporation of medium. No increase in related substances



1.4 Dissolution in Buffer pH 4.5 (HPLC)

102% dissolved after 2 hours. No observed degradation after 2 hours. Increase in impurities (0.1%) of Cladribine after 24 hours.



2 INTRINSIC DISSOLUTIONS

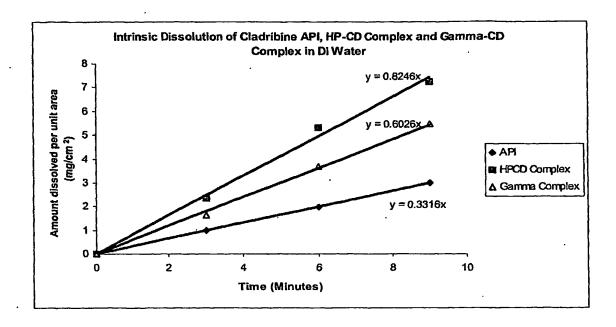
IDR of 0.1 mg/min/cm² corresponds to solubility of 1 mg/ml.

Cilag estimate solubility of 5mg/ml in water

IDR of API in DI water: IDR of Gamma-CD complex in DI water: 0.3316 mg/min/cm² 0.6026 mg/min/cm²

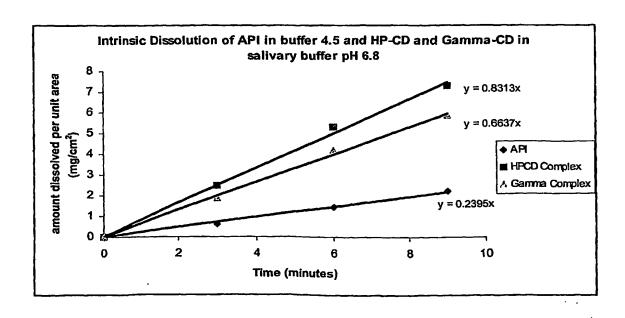
0.8246 mg/min/cm²

IDR of HP-CD complex in DI water:

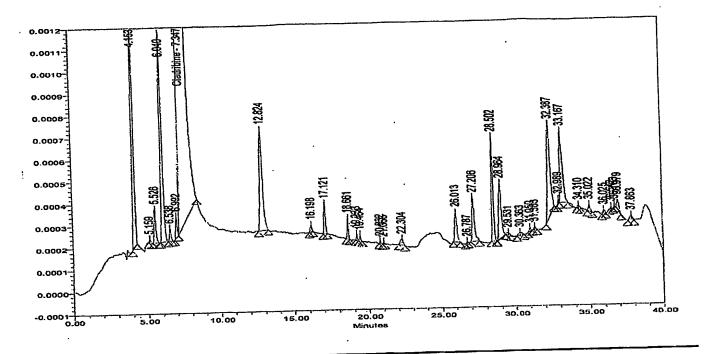


IDR of API in phosphate buffer pH 4.5: IDR of Gamma-CD complex in salivary buffer pH 7.0: IDR of HP-CD complex in salivary buffer pH 7.0:

0.2395 mg/min/cm² 0.6637 mg/min/cm² 0.8313 mg/min/cm²



3. API RELATED SUBSTANCES



Name	Specification	RRT	Cilag Assay	IVAX Assay
2-Amino-2 deoxyadenosine (Impurity B)	NMT 0.3%	0.563	0.200	0.060
2-Chloro-adenine (Impurity D)	NMT 0.3%	0.701	<0.1	0.002
2-Methoxy-2-deoxyadenosine (Impurity E)	NMT 0.2%	0.821	0.200	0.082
2-Chloro-9-(2 deoxy-α-D- ribofuranosyl)-adenine	NMT 0.2%	0.951	<0.1	0.01
(Impurity F) Cladribine	98% - 102%	1.000	99.8	98.5
Unknown 1	NMT 0.1%	1.763		0.088
Unlnown Impurity RRT (Cilag RRT) = 1.85	NMT 0.2%	1.85		ND
Impurity G	NMT 0.1%	2.123		ND
RWJ-47753-000	NMT 0.1%	3.877 -		0.043
RWJ-47754-000	NMT 0.1%	4.511		0.056
TOTAL IMPURITIES	NMT 1.0%		0.6%	0.3%

4. FINISHED PRODUCT RELATED SUBSTANCES

Name	RRT	Specification	RDT0385 (Fludaribine formulation)	RDT0398a (Carbomer formulation)	RDT039 (Cyclode formulat
2-Amino-2 deoxyadenosine (Impurity B)	0.563	NMT 0.3%	0.059	0.067	0.056
2-Chloro-adenine (Impurity D)	0.701	NMT 0.3%	0.002	0.002	0.002
2-Methoxy-2- deoxyadenosine (Impurity E)	0.821	NMT 0.2%	0.083	0.093	0.076
2-Chloro-9-(2 deoxy-α- D-ribofuranosyl)- adenine (Impurity F)	0.951	NMT 0.2%	0.010	0.012	0.009
Cladribine	1.000	98% - 102%	96	114	90
Unknown 1	1.763	NMT 0.1%	0.086	0.101	0.082
Uninown Impurity RRT (Cilag RRT) = 1.85		NMT 0.2%	,		
Impurity G	2.123	NMT 0.1%	0.001	0.000	0.000
RWJ-47753-000	3.877	NMT 0.1%	0.042	0.050	0.039
RWJ-47754-000	4.511	NMT 0.1%	0.049	0.059	0.047
TOTAL IMPURITIES		NMT 1.0%	0.33%	0.38%	0.24%

5. ASSAY AND RELATED SUBSTANCES OF FREEZED DRIED COMPLEX RAW MATERIAL AND TABLETS

Identity	Chemical Name	' RRT	Gamma – CD Raw Material	HP-β-CD Raw Material	FD02 (5mg Gamma- CD Tablets)	FD03 (5mg HPCD Tablets)
Imp B	2-Amino-2'- deoxyadenosine	0.54	0.28	0.19	0.31	0.29
Imp D	2-Chloroadenine	0.73	<0.05	ND	ND	ND
Imp E	2-Methoxy-2'- deoxyadenosine	0.83	0.14	0.12	- 0.13	0.13
Imp F	2-Chloro-9-(2'- deoxy-α-D- ribofuranosyl)- adenine	0.93	ND	ND	ND	ND
API	Cladribine	1.00	108	100	105	102
Theoretical % Active in Complex	Cladribine		2.128	2.347		
Actual % Active in Complex	Cladribine		2.293	2.353		
Unknown	Not Known	1.89	0.06	0.09	0.07	0.07
RWJ- 49616-000	Not Known	2.60	ND	ND	ND	ND
Unknown	Not Known	3.06	<0.05	1.56*	<0.05	<0.05
Unknown	Not Known	3.43	0.05	0.07	0.08	0.06
RWJ- 47753-000	Not Known	3.90	ND	ND .	ND	ND
Unknown	Not Known	4.18	ND	ND	0.26	ND
Unknown	Not Known	4.39	ND	ND	0.98	0.31
Unknown	Not Known	4.63	ND	0.33	ND	ND
RWJ- 47754-000	Not Known	4.68	0.22	0.15	0.34	0.21
TOTAL			0.75	2.51	2.17	1.01

^{*} To be investigated. Possible solvent or carryover.

SUMMARY

No differences observed in assay for related substances for API and any formulations. Recommended PDA analysis on API also.

6. FORMULATIONS BASED ON FLUDARIBINE

Three 100g batches using Cladribine API have been manufactured using the following formulations:

Batch	RDT0385	RDI0398a	RDT0398b
	Mudaribine	Carboner	Cyclodextrin :
	Formulation =	Formulation	Formulation
Angredient/emg/batch	YESTERS		
Cladribine API	10.00	10.00	10.00
Hydroxypropyl B			41.79
Gyclodextrin.		于当46分钟: 2000年7月 1955 ·	
Carbomer 974P		20.00	
Avicel PH101 5	21.80	16.7	11.25
Lactose DC11	65.00	50.1	33.76
Grosacarmellose 💥	2.00	2.00	2.00
Sodium - La			_
Collidol Silicon	0.20	0.20	0.20
Dioxide 2			
Magnesium Sterate	1.00	1.00	1.00
a villotal	100.00	100.00	100.00

Measurement	RDT 0385	RDT0398a	
			Segue (Cyclodexum)
Average table (weight (mg)	100.1	101.1	103.3
Average/Hardness(Kp).		4.4	3.7
Friability (%)	0.18	0.03	0.18
##Thickness (mm)	2.86	3.24	2.92
Disintegration (min)	0.50	> 15.00	6.60

6.1 Fludaribine Formulation: RDT0385

• Assay - 101.4%

• CU - 100.5%, RSD = 3.17%

• UV Dissolution (0.1N HCl) - Max 91% 30 minutes.

• HPLC analysis carried out on dissolution in HCl showed breakdown of Cladribine into impurity D. Only 3% Cladribine remaining after 2 hours dissolution.

• UV Dissolution (buffer pH 6.8) - Slow release. 85% after 240 minutes

UV Dissolution (Water)
 Fast release. 101% after 2 hours.

6.2 Enteric-coated tablets: (Fludaribine Formulation). RDT0385b

- UV Dissolution in 0.1N HCl followed by buffer pH 6.8 7.0.
- 7% dissolution after 2 hours in acid, (min 5%, max 18%). On addition of pH 7.0 conditions dissolution increased to 97% after 2 hours (min 84%, Max 107%). After 4 hours in acid, dissolution was 116%.

6.3 20% Carbomer Formulation: RDT0398a

Results may be related to tablet weight i.e. heavier tablet gives higher dissolutions

• Assay - 113.9%

CU - 105.7%, RSD = 6.4%. One result at 123.1%
 UV Dissolution (0.1N HCl) - Max 80%, 240 minutes. Slow release profile

• UV Dissolution (buffer pH 6.8) - Slow release. 86% after 10 hours. 0.1%

Carbomer interference. Further HPLC analysis shows possible Carbomer peak at 4-5 minutes.

0.2% - 1.0%.

• UV Dissolution (Water) - Fast release. 97% after 2 hours.

6.4 Cyclodextrin Formulation: RDT0398b

Cyclodextrin formulation is sub-potent due to extra Mag Stearate added. Estimated potency at 95%.

• Assay - 89.9%

• CU - 83.2%, RSD = 3.3%

UV Dissolution (0.1N HCl)
 Max 83%, 48 minutes. Degradation occurs.

UV Dissolution (buffer pH 6.8) - Max 76%, 1 hour. No Cyclodextrin interference

UV Dissolution (Water)
 Max 86% after 1 hour.

SUMMARY

- Cladribine API is acid labile. Formulation needed to avoid acidic stomach conditions.
- No degradation observed in water, buffer pH 4.5 and buffer pH 6.8
- API IDR matches Cilag estimated solubility. Best IDR in water.
- Solubility issue in buffer pH 6.8. Dissolution values are less than assay results.
- Solubility does not seem to be a problem in water. Dissolution results matching assay and CU.
- Fludaribine formulation shows fast release in water and slow release in buffer pH 6.8.
- Carbomer formulation allows for slow release. Carbomer impurity (approx 1.0%) present in chromatography.

Some spurious CU results (121%) indicating possible processing problems with Carbomer 974P or high levels of Carbomer.

• Possible potency issue with Cyclodextrin formulation. Only getting 90% assay and dissolution. Immediate release in buffer and water.

7 BUCCAL AND GRANULE FORMULATIONS WITH DICLOFENAC API

Six batches using Diclofenac Sodium in place of Cladribine API were manufactured to explore the development of buccal / sublingual and mucoadhesive tablets as patentable cladribine formulations.

Formulation:

	RDT0399a	RDT03996	RDT0399d	RDT0399e	RDT03991	RDT0399g
	となっている いいかい はんけん	100 April 100 Ap	Granule		Charles and the second	CHE THE GOVERNMENT OF THE PARTY
	tablet	tablet	THE PARTY THE PARTY TO A STATE OF THE PARTY TO A STATE		(Carbopol	-(Carbopol-
	MARCH ROY		= 974P) (974P)	71 C)	= ≥/1G==
Ingredient/						
Diclotenac	10.00	10.00	10.00	10.00	10.00	10.00
Sodium CMC-	2.50	5.00			連合が	
Sorbitol' 3.3	87.00	84.50		逻辑整理	の記載を記述	
Carbopol 974P	學們也非常物	造程型量扩张	2.50	10.00	能重量。計劃	第3号层图 数
Carbopol 71 G	医直肠型	是加盟的是	2000年1000年1000年1000年1000年1000年1000年1000		2.50	10.00
Avicel PHIOL 35		世界思考是	86.80	79.30	医有异类形式	医型型
Avicel RH102		海军温度建定	是是如果是到	持門在可能	21.75	19.88
Lactose DCH		南盖阳射 2度	新建筑区第 图		65.25	59.63
Merosil 海型产品			0.20	0.20	四時不可見回記	是非常可能
Mag. stearate	0.50	0.50*	0.50	0.50	0.50	0.50

^{*}Extra 0.5mg/tablet added to minimise picking. RDT0399c was manufactured as RDT0399a placebo.

Physical parameters:

Measurement 2	# RDT0399a	RD T0399b	RDT03991	RDT0399g-
Tooling/shape	Concave	Flat /Concave	Concave	Concave
Average tablet weight (mg)	95.8	94.5	95.1	99.7
Average Hardness (Kp)	3.76	2.10	2.94	2.46
書記Friability (%)直次	1.35	0.60	0.00	0.00
Thickness (mm):	3.07	2.90	2.95	3.10
aDisintegration (min)	2min 34sec	4min 45sec	>15min*	>15min**

^{*}Tablet formed a soft globular mass with adhesive properties

NOTE: Diclofenac has solubility problems in 0.1N HCl. Diclofenac Na dissolves 16% - 20% in 0.1N HCl.

^{**} Tablet formed a globular mass with strong adhesive properties. Mass was dry in center after 15 mins.

7.1 Buccal / Sublingual:

RDT0399a + RDT0399b:

Manufactured using Sodium CMC at 2.5 - 5 % respectively.

- UV Dissolution of approx 70% after 10 hours in simulated saliva solution. 68% dissolution after 30 minutes.
- Assay of 70%.
- No obvious reason for low results.
- Poor taste from tablets. Possible Diclofenac Na taste. Recommend 2mg drug formulation per 100
 mg tablet to inhibit possible taste issues.

7.2 Mucoadhesive granule for HGC fill:

Carbopol 71G may offer better flow properties due to its granular nature which may alleviate possible processing problems.

RDT0399d:

NOTE:

Manufactured using Carbopol 974P at 2.5%.

5% dissolution in 0.1N HCl after 2 hours. 97% dissolution after 3 hours in pH 7.0 buffer.

RDT0399e:

Manufactured using Carbopol 974P at 10%.

• 6% dissolution in 0.1N HCl after 2 hours. 91% - 99% after 3 hours in pH 7.0

7.3 Mucoadhesive Direct compression tablet:

RDT0399f:

Manufactured using Carbopol 71G at 2.5%.

5% dissolution in 0.1N HCl after 2 hours. 76% after 3 hours in pH 7.0

RDT0399g:

Manufactured using Carbopol 71G at 10%.

• 2% dissolution in 0.1N HCl after 2 hours. 90% after 3 hours in pH 7.0

All tablet formulations flowed and compressed well.

The granulated product produced a good strong granule. Milled through a 0.075 inch comil screen.

7.4 Tablet within a tablet formulation:

Outer tablet coat used to protect Cladribine from acidic stomach conditions.

Dissolution in 0.1N HCL followed by buffer pH 6.8. Tablets completely dissolved in acid (86% - 95%) after 25 minutes. No advantage.

8 PHASE SOLUBILITY TESTING

Table 1. Solubility of cyclodextrins in water (g/100 ml)

Temperatur e (°C)		BCD	GCD	HPCD
20.0	10.1	1.55	23.2	360.0
25.0	13.0	1.85	30.0	
30.0	16.0	2.25	38.5	
40.0	25.6	3.52	63.5	

PROTOCOL FOR PHASE SOLUBILITY STUDIES OF CLADRIBINE IN PRESENCE OF CYCLODEXTRIN

Reported Solubility of Cladribine in Water is 5 mg/ml

TABLE 1

SOLUTION	Solution of CD,		DRUG ADDED
SYSTEMS	800 mg in 4ml B.soln		
A	2ml B. Soln	(400 mg)	25 mg
В	2ml B.soln. + 2ml D.Water	(200 mg)	25 mg
C	2 ml soln. B + 2 ml D. Water	(100 mg)	25 mg
D	2 ml soln. C + 2 ml D. Water	(50 mg)	25 mg
Е	2 ml soln. D + 2 ml D.Water * Use only 2 ml of solution for	(25 mg)* r testing	25 mg
F	2 ml D.Water	(0.0 mg)	25 mg

Cyclodextrin

B.soln. - Bulk Solution

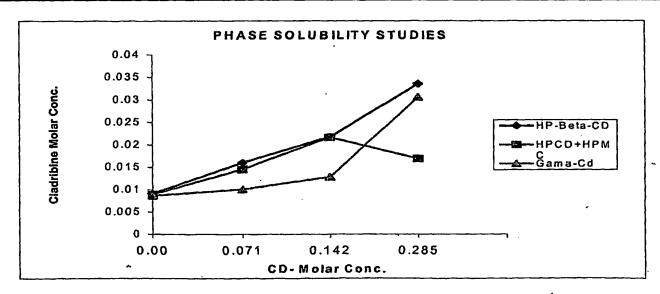
D. Water - Deionised Water

Method for preparation.

- 1. In screw capped vials take 2 ml Cyclodextrin solutions as mentioned in Table 1.
- 2. Add respective quantity of drug in each vial.
- 3. Allow the samples to sonicate for 30 minutes.
- 4. Remove the samples from sonicator and place on shaker for 8 hrs.
- 5. The sample after shaking is filtered to get clear supernant.
- 6. Analyse the sample by UV at 265 nm wavelength.

RESULTS:

CD Conc.	Conc. Cladribine –HP betaCD (Trial A)		Cladribine -HP betaCD + HPMC(0.1%) (Trial B)			Cladribine -gama- CD (Trial C)			
CD Conc.	Absorbance	mg/ml	Molar concn.	Absorbance	mg/ml	Molar concn.	Absorbance	mg/ml	Molar c
0.00	0.140	2.610	0.0091	0.137	2.550	0.0089	0.132	2.459	0.0086
0.018	0.169	3.139	0.011	0.146	2.711	0.0095	0.1352	2.519	0.0088
0.035	0.191	3.554	0.0124	0.175	3.262	0.0114	0.1531	2.852	0.0100
0.071	0.245	4.570	0.016	0.223	4.149	0.0145	0.1542	2.873	0.0101
0.142	0.333	6.211	0.0217	0.332	6.185	0.0216	0.1965	3.661	0.0128
0.285	0.514	9.581	0.0335	0.259	4.831	0.0169	0.4688	8.733	0.0306



Observations:

- The best solubility results are obtained with HP-beta CD as complexing agent.
- With HP-beta CD + HPMC (0.1%) results are similar to HP-beta CD, at higher concentration fine precipitation was observed in the vials at the end of the study.
 - Absorbance of this sample is low and indicates precipitation of solubised drug
- Absorbance with Gama-Cyclodextrin is low as compared with HP-beta CD.
- Ball park solubility of 9.581 mg/ml in comparison to 5 mg/ml solubility with API alone.

SUMMARY

- Cyclodextrin/Cladribine complex showed increased Cladribine solubility
- Complex sent for freeze-drying.
- Cladribine API ground to decrease particle size (10g)
- Process buccal and sublingual tablets using freeze-dried material Issues regarding taste and poor assay, dissolution on previous buccal tablets. Information on buccal formulation work in Miami.
- Continued investigation into oral dosage formulations:
 - 1. Tablet-within-tablet:
 High viscosity HPMC in outer formulation for protection against acidic stomach conditions.
 - 2. Soft gel capsule: 10g API sent to Czechslovakia for trials.
 - 3. Dry emulsion formulation:

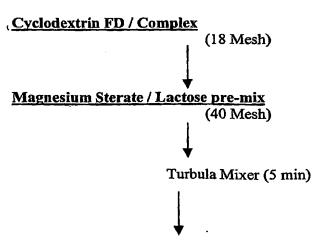
 Dummy emulsion to be made with freeze-dried sample

9 CLADRIBINE FREEZE-DRIED CYCLODEXTRIN COMPLEXES

9.1 Cyclodextrin Complex Formulations for Buccal/Sublingual Dosage forms

	PRODUCT				Gamma CD	
						= +Cladribine
			Tablets			Complex Tablets
月四三三 三					Complex -	
				THE AND RESIDENCE AND ADDRESS OF THE	Lablets 2	
China and the same of the same	Batch No.					CRDIT 0418D
Codes	Ingredient		Mg-/ Tablet	Mg/Tablet	Mg/Jable	Mg/, Tablet
FD-01	Gamma -CD	N/A	213	213	-	-
FD-02	Gamma-CD	N/A	-	-	235	-
	+Cladribine					
FD-03	HPCD + Cladribine	N/A	-	-		218
RE0484	Sorbitol	1F290		5.0	-	-
RE0541	Magnesium Stearate	1C130	2.0	2.0	2.0	2.0

9.2 Manufacturing Process



Manesty Single station F-press (220 mg, 10.0 mm round concave UP/ Flat Bevelled LP)

OBSERVATIONS.

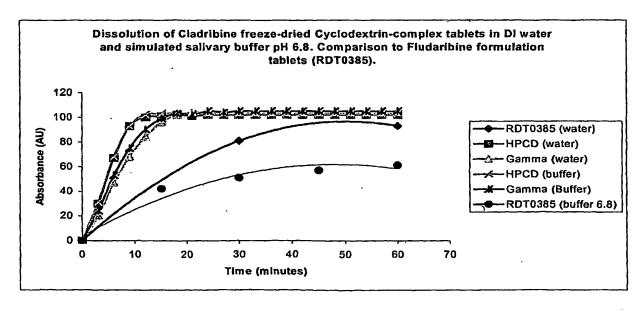
Flow and compressibility good for all fractions.

No picking noticed

9.3 Physical Parameters

- Average weight: A) 215 mg, B) 220 mg, C) 237mg, D)220mg.
- Average Hardness: 3- 4 Kp
- Thickness: 3.2 mm 3.4 mm
- Disintegration Time: 6 7 minutes (Water/Simulated Saliva Buffer)

9.4 Dissolution profiles of freeze-dried buccal tablets in water and simulated salivary buffer solution



Simulated Saliva Solution: 2.38g Na₂HPO₄, 0.19g KH₂PO₄ and 8g NaCl in 1 litre of distilled water, pH 6.75, at 37°C

9.5 Results

• Increased Dissolution time.

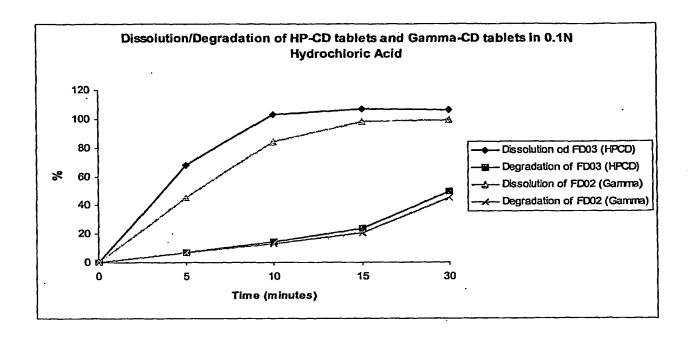
HP-CD. 100% dissolution in salivary buffer after 10 minutes. Gamma-CD. 100% dissolution in salivary buffer after 15 minutes

HP-CD. 100% dissolution in water after 10 minutes. Gamma-CD. 100% dissolution in salivary buffer after 15 - 18 minutes

Increased Solubility.

100% dissolution attained for both tablet types in both buffers. Comparison to Fludaribine formulation dissolution in water and buffer show faster dissolution and greater solubility.

9.6 Dissolution and Degradation profiles of freeze-dried Cladribine-Cyclodextrin complex buccal tablets in 0.1N HCl



- Degradation of Cladribine peak to Impurity D observed. 10 15% after 10 minutes. 100% dissolution after 10 15 minutes.
- By optimising complexation, we can further inhibit acidic degradation of the drug in the stomach whilst increasing drug availability for absorption.